REMARKS

Claims 7, 9, 10, 12 are pending. Claim 7 has been amended to further recite that there is no target nucleic acid in the claimed composition. Support for the amendment can be found throughout the specification, *e.g.*, page 4, lines 14-15 and page 5, lines 24-36. Claim 11 has been cancelled without prejudice or disclaimer. Claim 7 has also been amended to change "the target sequence" to "said target nucleic acid" so as to be consistent with its antecedent basis. Claim 12 has been amended to remove dependency on cancelled claim 11. No new matter has been introduced by way of these amendments. Applicants respectfully request reconsideration of the claims in light of the amendments presented above and the remarks presented below.

Rejection under 35 U.S.C. § 102(b)

Claims 7 and 9, 10, and 12 stand rejected under 35 U.S.C. § 102(b) as anticipated by Nilsson *et al.* (Science 265:2085-2088 (1994)). In the Final Office Action and the Advisory Action, the Examiner rejects these claims on the belief that the cited reference teaches the same composition as claimed in the instant invention. Applicants respectfully traverse the rejection.

Amended claim 7 claims a composition for targeting double stranded nucleic acids, said composition comprising a pharmaceutically acceptable carrier and an effective amount of a padlock probe oligonucleotide having two free nucleic acid end parts which are at least partially complementary to and capable of hybridizing with at least substantially neighboring respective regions of a double stranded target nucleic acid so that the padlock probe can be circularized by joining said free end parts to thereby catenate with said target nucleic acid, wherein said target nucleic acid is directly inhibited and wherein said composition does not contain said target nucleic acid.

The cited reference teaches the use of the probe to identify DNA clones in genomic libraries or fragments in blots of the whole genome or for *in situ* analysis of chromosomes. For example, Figure 4, to which the Examiner cites, teaches the use of padlock probe for the *in situ* hybridization detection of a chromosome 12-specific repeated sequence. *See Nilsson* at 2087. In this example, Nilsson discloses hybridization of denatured chromosome 12 with a biotinylated circularizable probe, followed by a brief wash in 10mM tris, pH 7.5, 10mM Mg(Ac)2, 50 mM

KAc, 10mM ATP buffer, and subsequent ligation in the same wash buffer with the addition of T4 DNA ligase. *Id.*

The instant invention is distinguishable from the cited reference. First, claim 7 recites in relevant parts "a composition comprising a pharmaceutically acceptable carrier and [a]... padlock probe oligonucleotide...wherein said composition does not contain said target nucleic acid." Nilsson's disclosure does not teach a composition that meets these requirements. Specifically, in the hybridization step, Nilsson teaches a DNA and probe composition in formamide, SSC, and salmon sperm DNA. In the wash step, Nilsson teaches a DNA-probe composition that is subjected to a "brief wash" in buffer. In the ligation step, the DNA-probe composition is ligated in the same wash buffer with the addition of T4 DNA ligase. At no point in *Nilsson* is there a teaching of a composition that contains a pharmaceutically acceptable carrier, a padlock probe, and no target nucleic acid. In fact, the target nucleic acid is always present in the compositions of Figure 4. Thus, Nilsson's disclosure does not anticipate the composition claimed in the instant invention. On this basis alone, the rejection should be withdrawn.

The Examiner also alleges that Nilsson's disclosure of a ligation buffer constitutes "a pharmaceutically acceptable carrier" as presently claimed. The Examiner supports this contention by citing additional references (*Rajagopalan, Shelley, Mills,* and *Rapaport*) as extrinsic evidence for the proposition that the ligation buffer in *Nilsson* is inherently a pharmaceutically acceptable carrier. Applicants respectfully disagree.

When the cited reference is silent about an alleged inherent characteristic, the gap in the reference may be filled with extrinsic evidence, such extrinsic evidence, though, must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. *Continental Can Co. v. Monsanto,* 20 USPQ2d 1746, 1748 (Fed. Cir. 1991). Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. *In re Oelrich,* 212 USPQ 323, 326 (CCPA 1981) (quoting *Hansgirg v. Kemmer,* 40 USPQ 665, 667 (CCPA 1939)).

Here, the Examiner has cited four additional references, each teaching a component of Nilsson's ligation buffer as a pharmaceutically acceptable carrier. Not one of the references, however, discloses all the components of Nilsson's ligation buffer as a pharmaceutically acceptable carrier. Thus, the Examiner has not shown that the ligation buffer is intrinsically a pharmaceutically acceptable carrier. By analogy to *Oelrich*, it is not sufficient to show inherency simply because individual components of Nilsson's ligation buffer are disclosed in each of the four references as one of a multiplicity of other molecules that can be used as pharmaceutically acceptable carriers.

In addition, *Nilsson* does not teach a composition that contains the ligation buffer as cited by the Examiner. The cited buffer is used in Nilsson to briefly wash the hybridized DNA-probe composition. *See* Figure 4. The use of the buffer in a wash step would not constitute a composition as presently claimed. Even assuming that the wash step can be included as a composition with the DNA and the probe, the cited reference would not anticipate the instant invention because claim 7 recites the composition does not contain the target nucleic acid.

Accordingly, Applicants submit that *Nilsson* does not anticipate the present claims because the reference does not teach the pharmaceutically acceptable carrier as claimed in the instant invention. Also, *Nilsson* does not disclose the claimed composition where the target nucleic acid is *not* present. Applicants respectfully request withdrawal of the rejection.

Rejections under 35 U.S.C. § 112, first and second paragraphs

Claims 11 and 12 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which the applicant regards as the invention. Claims 11 and 12 also stand rejected under § 112, first paragraph as failing to comply with the written description requirement. Applicants have cancelled claim 11 and amended claim 12 to remove its dependency on cancelled claim 11, thus rendering the rejections moot.

CONCLUSION

Applicants submit that the claims are now in condition for allowance and early notification to that effect is respectfully requested. Please direct any calls in connection with this application to the undersigned at (415) 781-1989.

Respectfully submitted,
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BY: _____

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